EHA Overview from Joshua Richter, MD

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Hello and welcome to *Managing Myeloma,* I am Dr. Joshua Richter. We are pleased to present highlights in multiple myeloma from the 2018 European Hematology Association's Annual Congress. Today we are going to talk about some of the themes of studies that were presented at this congress, as a lot of data was presented across myeloma and other disease states. Five big things that came across this year in multiple myeloma were: the three- versus two-drug regimens; optimizing carfilzomib-based chemotherapy regimens; new anti-CD38 monoclonal antibodies; a new wave of oral therapies for multiple myeloma; and the importance of minimal residual disease (or MRD) testing.

First off, the three- versus two-drug regimens. There was a number of studies published across the last few years demonstrating the superiority of three-drug regimens versus two-drug regimens in the relapsed and refractory setting of multiple myeloma. This year's 2018 EHA was no different. There were two big studies that were presented, the ELOQUENT-3 study as well as the OPTIMISMM study. In the ELOQUENT-3 study, we saw the three-drug regimen of elotuzumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone.[1] Patients here had more than two lines of prior therapies and were randomized between the two different groups. There were improvements, of course, in progression-free survival and, although it is still immature data, a trend towards improvement in overall survival with the three-drug regimen over the two-drug regimen. With the OPTIMISMM study, we saw the three-drug regimen of pomalidomide-bortezomib-dexamethasone versus bortezomib-dexamethasone.[2] Here the patients were slightly less heavily pretreated, typically one to three prior regimens. Again, the three-drug regimen was superior; and in those patients with only one prior regimen, we see progression-free survivals that are extremely long and approaching two years.

Regarding the optimization of carfilzomib-based therapies, there were a number of trials presented at EHA this year. Notably throughout its approval, carfilzomib has enjoyed a variety of different applications across multiple myeloma, across different infusion times, different dosing schedules, and different doses themselves. Here at EHA, we got some more clarification about optimal ways to administer carfilzomib in the relapsed and refectory setting for multiple myeloma. Three trials of note were the A.R.R.O.W. trial (daratumumab-carfilzomib-dexamethasone) and the once-weekly KRd (carfilzomib-lenalidomide-dexamethasone) trial. In the A.R.R.O.W. trial, we capitalized on the information that we have learned from the CHAMPION-1 trial,[3] where the maximum tolerated dose was found to be 70 mg/m² as a weekly dosing for

carfilzomib. Here in the A.R.R.O.W. trial, we saw a head-to-head comparison of standard-dose carfilzomib 20/27 at a twice-weekly dosing versus 20/70 as a once-weekly dosing.[4] We saw superiority of overall response rates, superiority in progression-free survival, and improved deeper responses, with a higher CR rate seen in the once-weekly versus twice-weekly dosing. Of course, people's concern is for cardiac toxicity when the dose of carfilzomib is increased to these heights. However, there was only minimal cardiac toxicity seen across both cohorts. We also looked into dosing with carfilzomib and daratumumab. Daratumumab is currently approved in the upfront setting in combination with VMP[5] (bortezomib-melphalan-prednisone) and in the relapsed/refractory setting as a single agent or in combination with lenalidomide, bortezomib, or pomalidomide.[6] Here we saw data presented on daratumumab plus carfilzomib in lenalidomide-refractory patients.[7] Eighty-five carfilzomib-naïve patients with one to three prior lines of therapy were treated, and this was associated with extremely high response rates of over 80%. For those patients who were not lenalidomide-refractory, it was even higher at 86%. We also saw a trial with once-weekly carfilzomib, lenalidomide, and dexamethasone. Although twice-weekly carfilzomib, lenalidomide, and dexamethasone is approved based off of the ASPIRE trial,[8] here we saw the same approach of using once-weekly carfilzomib, either at 56 mg/m^2 or 70 mg/m^2 in combination with lenalidomide and dexamethasone. The combination was well-tolerated, the maximum tolerated dose was not reached, and overall response rates were approximately 90%.[9]

With regard to new anti-CD38 monoclonal antibodies, there is an exciting repertoire of drugs in the pipeline. Daratumumab has become a staple of our management of myeloma patients; however, a newer CD38 antibody, isatuximab, has now presented newer data in combination. There are two trials in particular: one with isatuximab plus pomalidomide, and one with isatuximab plus carfilzomib. In both of these trials, patients who have relapsed or refractory multiple myeloma who had at least two prior therapies were treated with the combinations. There were very high response rates and they were quite durable.[10,11] We are excited to see how this drug will pan out and it is hopefully nearing approval.

With the newer therapies, we are now seeing a wave of oral bioavailable therapeutics entering the myeloma landscape. Although we already have the IMiDs and histone deacetylase inhibitors, we are now seeing new types of oral therapies entering the realm of our myeloma repertoire. In particular, we have seen the advent of selinexor and venetoclax. This year at the 2018 EHA Congress, we saw data presented from the selinexor-bortezomib-dexamethasone trial. This is representative of the ongoing BOSTON trial which is a registration trial seeking to lead towards the approval of the combination of selinexor-bortezomib-dexamethasone. Here we see selinexor, an oral bioavailable first-in-class SINE (selected inhibitor of nuclear export), combined with bortezomib-dexamethasone being established as a once-weekly dosing schedule with once-weekly dexamethasone, once-weekly bortezomib, and once-weekly oral selinexor.[12] The combination is both well-tolerated and highly effective. Furthermore,

the weekly dosing avoids excessive dexamethasone exposure and reduces the frequency with which patients need to come to clinic. Venetoclax has come into the realm of myeloma as a very important potential new avenue of treatment. This year, Kaufman, et al., in abstract PS1317 presented venetoclax plus or minus dexamethasone in patients with multiple myeloma having an 11;14 translocation.[13] Venetoclax is an orally bioavailable BCL-2 inhibitor, and it appears to be active in patients who have both high expression of BCL-2 and a 11;14 translocation. In this trial, we saw 50 patients; 30 treated with venetoclax alone and 20 treated with venetoclax and dexamethasone. The overall response rate for the entire group was 50%, with an overall response rate of 65% in the venetoclax-dex arm and 40% in the venetoclax alone arm. What is interesting is that the median time to progression was 8.3 months in the venetoclax alone arm and 12.5 months in the venetoclax plus dexamethasone arm. Again, these are patients who are heavily pretreated, with many of the patients having more than four prior lines of therapy. In fact, of the 50 patients treated, the median lines of prior therapy was four. What is further important about this trial is that we started to understand whether or not the expression of BCL-2 within the bone marrow space affects a patient's response to venetoclax. As has previously been demonstrated in the venetoclax alone arm, patients who had higher BCL-2 expression in the marrow had a higher overall response rate to monotherapy with venetoclax. In this trial, the overall response rate was 89% versus 27% in the venetoclax alone arm for patients with high versus low BCL-2 expression. This difference, however, was not demonstrated in the combination arm with venetoclax and dexamethasone where the BCL-2 expression in the marrow did not affect the rate or depth of response.

The other interesting thing that was seen at EHA this year were studies focusing on the benefit and utility of MRD (or minimal residual disease) testing. This technology has been used across clinical trials and is slowly working its way into the clinic to become part of how we manage our day-to-day patients. Two trials that I thought were quite interesting were focused on the utility of predicting outcome based on MRD rates. One was a study that looked at the impact of sustained MRD at the 12-month mark to predict better outcomes. There has been data to date supporting the predictive value of MRD negativity rates early in the disease course, as in following induction at 3 months. We are now looking at following MRD at multiple timepoints: at 3 months and now 12 months; and this trial confirmed that patients who not only achieve minimal residual disease negativity but maintain it at the 12-month mark will have improved outcomes.[14] This technology and ability to look into this may provide guidance in terms of how to manage our long-term patients once they achieve MRD negativity and sustain it. Another study focused on combining MRD evaluation with PET scans. In this study, patients were evaluated with MRD testing as well as PET/CT testing along the course of their disease. In this study, 148 patients were evaluated and they were classified as being MRD-negative and PET-negative at evaluations, MRD-positive and PET-negative, or PET-positive (because the patients who were PET-positive did not show any difference in their MRD negativity states). When looking at the different groups, the patients who were PET-positive had a median

progression-free survival of 28 months.[15] However, when both the PET/CT and the MRD evaluations were negative, the median progression-free survivals were not yet reached. In general, this is providing a multimodality approach to evaluate patients both in terms of disease bulk on imaging and bone marrow disease burden. Together we can combine these modalities and not only predict which patients are going to have better outcomes, but hopefully evolve to use this technology to predict who needs further therapy, who does not need further therapy, who should continue on maintenance, and which patients may need additional therapy to achieve deeper remissions.

Taking all of the new data into account, I think there are a variety of things that we can look forward to in the coming year that we can incorporate into the management of our day-to-day myeloma patients. First off, the utilization of three-drug regimens over two-drug regimens. While not all patients are going to be eligible for three-drug regimens based on performance status, frailty or comorbidities, it continues to be the recommendation to try to put a patient on a three-drug regimen if possible; and with newer and newer drugs on the market, this may become easier and easier.

Regarding the use of carfilzomib, we now see that there are more and more ways to utilize the drug in the relapsed and refractory setting; and while some of the previous ways may not be optimal for our patients, we are now going to see new ways that we can incorporate this drug into the management of our patients that may open it up to a further array of eligible candidates. Regarding oral therapies, the incorporation of drugs like selinexor and venetoclax may soon be working their way into our clinic and it is important to be aware of their impending arrival. Selinexor is not yet FDA-approved but is likely to be FDA-approved within the next 6 to 12 months. Although venetoclax is not FDA-approved in multiple myeloma, it is an FDA-approved therapy for certain types of lymphoma and represents a potential option for patients with 11;14 translocations or BCL-2 overexpression on the marrow who are running out of other therapies. Regarding MRD testing, I think this is going to have to become part of our day-to-day management of myeloma to give us better insight into which patients need further therapy and which do not. As MRD testing is working its way as a potential component of FDA approvals for therapies, we are going to have to start doing more bone marrow evaluations on our patients to make sure that we are hitting those timepoints of response and are reacting appropriately. Much in the same way that CML makes it incumbent upon us to follow certain landmarks of response, the same may be true in the coming years for multiple myeloma as well. Keep a lookout for these and other innovations in the coming years.

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